

## Relationships between NT-proBNP and novel biochemical parameters and increased cardiovascular risk in COVID-19

NT-proBNP levels and novel inflammatory biomarkers in COVID-19

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### Abstract

**Aim:** The ongoing pandemic of coronavirus disease 2019 (COVID-19) infection has been declared a global emergency. Although most people have had mild illness due to this infection, some patients are seriously affected with complications particularly involving the respiratory and cardiovascular systems. Although respiratory system involvement is in the foreground, cardiovascular complications result in worse clinical outcomes. The aim of this study is to compare the levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios, which are accepted as markers of negative outcomes in cases of cardiovascular diseases, of patients with COVID-19 and healthy subjects and reveal the increased risk of cardiovascular disease in patients with COVID-19.

**Material and Methods:** This prospective study was designed in a single center and included 33 patients with COVID-19 (Group 1) and 33 healthy subjects selected from among healthcare professionals (Group 2). The NT-proBNP levels and neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios were compared between the groups.

**Results:** NT-proBNP levels, neutrophil-to-lymphocyte ratios, and platelet-to-lymphocyte ratios were statistically significantly higher in the patients with COVID-19 ( $p < 0.0001$ ) and lymphocyte-to-monocyte ratios were statistically significantly lower in the same group ( $p < 0.0001$ ).

**Discussion:** Cardiovascular manifestations result in worse outcomes in patients with COVID-19 even though the disease primarily affects the respiratory system. Early detection of this clinical situation and the taking of precautions have vital importance in the progress of the disease. The NT-proBNP level and neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios are inexpensive, easy, fast, and reproducible parameters that can be used in the determination of probable cardiovascular events that may develop during COVID-19 and enable early optimal treatment strategies for patients.

### Keywords

Cardiovascular Disease; COVID-19; NT-proBNP; Lymphocyte-to-Monocyte Ratio; Neutrophil-to-Lymphocyte Ratio; Platelet-to-Lymphocyte Ratio

DOI: 10.4328/ACAM.20797 Received: 2021-07-27 Accepted: 2021-09-10 Published Online: 2021-09-14 Printed: 2021-09-15 Ann Clin Anal Med 2021;12(Suppl 4): S529-533

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## Introduction

Coronavirus disease 2019 (COVID-19) was accepted as a public health emergency situation and declared a pandemic by the World Health Organization (WHO) at the beginning of March 2020 [1]. The clinical properties of COVID-19 are mostly related to respiratory system symptoms including fever, cough, pharyngodynia, and complications related to pneumonia and acute respiratory distress syndrome. Most patients with COVID-19 have a good prognosis, but critical patients might rapidly develop acute respiratory failure, acute respiratory distress syndrome, multi-organ failure, and other potentially fatal complications including neurological deficits, gastrointestinal disorders, renal failure, myocarditis, and acute coronary syndromes [2].

Acute cardiac injury and arrhythmia were reported in 7.2% and 16.7% of cases, respectively, in a single-center study consisting of 138 COVID-19 patients [3].

Several markers can be used in the assessment of cardiac injury among patients with COVID-19. One of these markers is N-terminal pro-brain natriuretic peptide (NT-proBNP), which is released as a response to increased ventricular wall tension and shows reduced left ventricular systolic function and poor prognosis in cardiac involvement [4].

Inflammation is one of the most important causes of vascular damage. Alongside various other markers that indicate inflammation, neutrophil-to-lymphocyte (Neut/Lym), lymphocyte-to-monocyte (Lym/Mono), and platelet-to-lymphocyte (Plt/Lym) ratios are recently introduced biochemical markers for inflammation-associated diseases including vascular injury [5].

Our study is unique in terms of comparing NT-proBNP levels and Neut/Lym, Lym/Mono, and Plt/Lym ratios between patients with COVID-19 and healthy subjects in the same study. In doing so, we aim to reveal the increased risk of cardiovascular diseases among patients with COVID-19 using these parameters.

## Material and Methods

Between October 2020 and January 2021, 33 adult patients diagnosed with COVID-19 and 33 healthy subjects were included in this study. Diagnosis of the disease was performed via RNA detection from nasopharyngeal secretions by real-time reverse-transcriptase polymerase chain reaction (PCR) and by chest computed tomographic (CT) scanning using the diagnostic criteria defined by the WHO interim guidelines. Healthy subjects consisted of voluntarily participating healthcare professionals without any chronic diseases such as cardiovascular disease, cerebrovascular disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, or any kind of neoplasia; they were all employed at the institute in which the study was designed. The possibility of COVID-19 among control subjects was excluded with the absence of viral RNA in PCR test results. Written informed consent was obtained from all participants and this single-center prospective study was approved by the clinical ethics committee of the institution (Decision No: 2020/369) and performed in compliance with the Declaration of Helsinki.

Data of the patients including demographic characteristics (age, gender), comorbidities, laboratory findings, radiographic

images, electrocardiographic findings, and treatments were collected from hospital records. Laboratory tests included complete blood count, renal and liver function analyses, and levels of C-reactive protein (CRP), D-dimer, and NT-proBNP, which were measured within 24 hours of admission. Complete blood cell counts and automated differential counts were determined with an automated hematology analyzer (CELL-DYN 3700, Abbott, Germany), which provided total white blood cell count and platelet, neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts/mL. The baseline Neut/Lym, Lym/Mono, and Plt/Lym ratios were calculated by dividing the absolute counts of those parameters. An electrochemiluminescence-based immunoanalytical system (Elecsys 2010, Roche Diagnostics Ltd., Mannheim, Germany) was used to determine plasma levels of NT-proBNP. Patients with elevated NT-proBNP were hospitalized for close follow-up to prevent or quickly intervene in the case of probable cardiac disorders that could develop, and all patients underwent transthoracic echocardiography. Favipiravir, hydroxychloroquine sulfate, levofloxacin, and enoxaparin sodium were begun after blood collection as initial therapy for all patients according to the Turkish Ministry of Health's guidelines for COVID-19 therapy.

Exclusion criteria of the patients with COVID-19 were any diagnosed cardiovascular and cerebrovascular diseases, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, neoplasia, age younger than 18 years, and pregnancy. The primary end point of the study was the composite of death or the requirement for mechanical ventilation, admission to the intensive care unit, or extracorporeal membrane oxygenation. Physical examination included cardiac auscultation and blood pressure measurements, electrocardiography, echocardiography, and laboratory findings were used to detect any cardiovascular disease for the exclusion criteria. The presence of other exclusion criteria was determined by anamnesis and national hospital records together with physical examination and laboratory tests.

Participants were divided into two groups. Group 1 consisted of the patients with COVID-19 and Group 2 consisted of the healthy control subjects. NT-proBNP levels and Neut/Lym, Lym/Mono, and Plt/Lym ratios were compared between the groups.

### Statistical Analysis

All values were shown as mean $\pm$ SD or percentage. The distribution of all variables was checked with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for data with abnormal distribution. Otherwise, the differences between the mean values of the two groups were analyzed using the unpaired Student t-test. Gender distribution of the two groups was analyzed using the chi-square test. The Pearson test was used to assess the correlations, but Spearman correlation analysis was performed for correlation analysis of data with abnormal distribution. GraphPad InStat statistical software (version 3.05, GraphPad Software Inc., San Diego, CA, USA) was employed. Statistical significance was accepted at the level of 0.05.

## Results

Thirty-three patients with COVID-19 and 33 healthy subjects were included in this study. These participants were divided

into two groups. The demographic features and laboratory findings are summarized in Table 1. There were no statistically significant differences in terms of demographic features including age and gender between the groups.

**Table 1.** Demographic features and laboratory findings of the groups

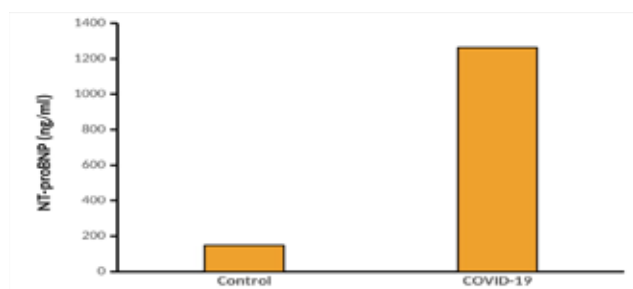
Parameters	Controls (n=33)	Patients with COVID-19 (n=33)	p
Age <sup>a</sup>	58.33±1.70	58.48±3.01	0.9655
Gender, n (%)			
Male	18 (54.55)	20 (60.60)	0.8053
Female	15 (45.45)	13 (39.40)	
NT-proBNP (pg/mL)	149.32±16.33	1262.67±394.93	<0.0001
WBC count (103/μL)	7.75±0.28	6.98±0.44	0.1467
Neutrophils (103/μL)	4.48±0.23	5.14±0.42	0.1782
Lymphocytes (103/μL)	2.40±0.11	1.29±0.09	<0.0001
Monocytes (103/μL)	0.63±0.03	0.50±0.04	0.0457
Platelets (103/μL)	265.67±11.45	525.76±36.96	0.2852
AST (U/L)	28.09±1.53	42.27±7.55	0.4302
ALT (U/L)	26.79±1.01	45.61±9.52	0.4378
AST/ALT	1.04±0.03	1.11±0.07	0.3349
Creatinine (mg/dL)	0.72±0.03	0.82±0.04	0.0543
D-Dimer (ng/mL)	0.54±0.03	0.83±0.11	0.0135
CRP (mg/L)	0.55±0.03	54.90±11.25	<0.0001
Neutrophil-to-lymphocyte ratio	2.04±0.18	4.55±0.49	<0.0001
Lymphocyte-to-monocyte ratio	4.17±0.27	2.71±0.20	<0.0001
Platelet-to-lymphocyte ratio	120.24±9.11	215.04±20.60	<0.0001

<sup>a</sup>Data are presented as mean±SEM. NT-pro BNP: N-Terminal pro-brain natriuretic peptide  
WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase  
CRP: C-reactive protein.

**Table 2.** Correlations between biochemical parameters in COVID-19 patients

Parameters	Correlation coefficient (r)	Coefficient of determination (r <sup>2</sup> )	p
NT-proBNP«Lymphocytes	-0.0498	0.0025	0.7831
NT-proBNP«Monocytes	0.0510	0.0026	0.7781
NT-proBNP«D-dimer	0.6780	0.4597	<0.0001
NT-proBNP«CRP	0.1722	0.0297	0.3378
NT-proBNP«Neutrophil-to-lymphocyte ratio	0.1608	0.0259	0.3714
NT-proBNP«Lymphocyte-to-monocyte ratio	-0.1272	0.0162	0.4806
NT-proBNP«Platelet-to-lymphocyte ratio	0.1103	0.0122	0.5412

NT-pro BNP: N-Terminal pro-brain natriuretic peptide, CRP: C-reactive protein.



**Figure 1.** Comparison of NT-proBNP levels between patients with COVID-19 and control group.  
NT-pro BNP: N-Terminal pro-brain natriuretic peptide.

There were also no marked differences between the groups for leukocyte, neutrophil, monocyte, and platelet counts or liver and kidney function tests. However, NT-proBNP levels were markedly elevated in COVID-19 patients ( $p < 0.0001$ ), as shown in Figure 1. NT-proBNP levels were 8.5 times higher in patients with COVID-19 than in the healthy control subjects. D-dimer ( $p = 0.0135$ ) and CRP ( $p < 0.0001$ ) levels and Neut/Lym ( $p < 0.0001$ ) and Plt/Lym ( $p < 0.0001$ ) ratios were also statistically significantly higher in Group 1. In contrast, the Lym/Mono ratio was found to be statistically significantly lower in Group 1 ( $p < 0.001$ ).

Correlations between ratios and biochemical parameters in patients with COVID-19 were also compared and the results are given in Table 2. We detected a positive correlation between only NT-proBNP and D-dimer levels.

**Discussion**

After the first described cases of pneumonia of unknown origin in Wuhan, China, SARS-CoV-2 rapidly became pandemic. Current epidemiologic studies suggest that about 80% of patients with COVID-19 have mild symptoms while 5% become critically ill, requiring mechanical ventilation [6]. Although the most common symptoms including fever, dry cough, fatigue, headache, and shortness of breath are associated with the respiratory system and complications are usually related to acute respiratory distress syndrome or pneumonia, cardiovascular involvement is also an additional clinical problem to consider in cases of COVID-19 [7]. Acute cardiac injury rates during this illness range between 7% and 28% in different studies, significantly increasing COVID-19-associated complications and mortality [8]. Increased affinity of SARS-CoV-2 to the angiotensin I converting enzyme 2 (ACE2) receptor, which is expressed mainly in the lungs and other tissues including vascular endothelial cells, was shown in previous studies. The ability of SARS-CoV-2 to directly infect endothelial cells is one of the strange features of the virus and distinguishes it from most other infectious diseases [9].

Several mechanisms were suggested for the myocardial damage of SARS-CoV-2, including direct damage by the virus, systemic inflammatory responses, destabilized coronary plaque, and aggravated hypoxia. Viral entry into the myocardium and arteries via the ACE2 receptor induces ACE2 downregulation and renin-angiotensin-aldosterone system dysfunction, which leads to heart dysfunction and pneumonia progression [10]. The activation and overproduction of inflammatory cytokines can also induce necrosis and apoptosis of cardiomyocytes. Imbalance of T helper 1 and T helper 2 responses triggers a cytokine storm in patients with COVID-19, which may cause myocardial injury [7]. High oxygen demand due to fever and tachycardia and insufficient oxygen supply due to hypoxemia and respiratory failure are usually seen during the infection, which could result in a type 2 myocardial infarction [11].

A variety of types of cardiovascular involvement, including heart failure, myocarditis, pericarditis, acute coronary syndrome, and arrhythmias, were described in previous studies. New-onset heart failure was observed in hospitalized and intensive care patients with COVID-19 at rates of 25% and 30%, respectively, although these individuals had no history of heart failure [12].

Proinflammatory cytokines and recruitment of proinflammatory macrophages and granulocytes in the blood stream lead to severe inflammatory storms and, in combination with increased metabolic demand, may cause cardiac depression and either new-onset heart failure or acute decompensation of chronic heart failure [13]. Viral infections have been shown as one of the most common infectious causes of myocarditis and pericarditis. In spite of widely reported myocarditis cases due to SARS-CoV-2, limited data have been published on patients with COVID-19 who developed pericarditis and pericardial effusion [14]. The myocardium and pericardium being directly affected via the virus replicated and disseminated through the blood or the lymphatic system from the respiratory tract may be the probable mechanism of these complications [2]. In patients infected with SARS-CoV-2, increased interleukin-6 and D-dimer levels, indicating the augmented coagulation response, are linked with plaque instability and occurrence of acute coronary syndrome [15]. According to the study designed by Bangalore et al. [16], 9 of 18 patients with COVID-19 who had ST-segment elevation on electrocardiogram underwent coronary angiography. Three of them were found to have obstructive disease, which indicates that hypoxic injury, coronary spasm, microthrombi, and endothelial injury may also result in acute coronary syndrome without any occlusion in patients with COVID-19.

Cardiac arrhythmias and cardiac arrest are other common manifestations observed in COVID-19 patients, but specific types of arrhythmia were not described. Atrial fibrillation, high-grade atrioventricular tachycardia, polymorphic ventricular tachycardia, and pulseless electrical activity arrest are the common disorders mentioned in the literature. Hypoxemia and electrolyte disturbances are thought to be responsible for arrhythmogenicity [17].

Several markers can be used in the detection of heart injury, including hs-cTnI, NT-proBNP, CK-MB, myoglobin, and lactate dehydrogenase. The B-type natriuretic peptide (BNP) was first isolated from the brains of pigs; however, it was soon found to originate mainly from the heart, being a cardiac hormone, and it is synthesized as a prohormone (proBNP) consisting of 108 amino acids. Upon secretion, this propeptide is split into its biologically active form, BNP, and the remaining NT-proBNP. Although plasma concentration and cardiac production of NT-proBNP are very low under normal conditions, increased ventricular wall stretching, neurohormonal activation, and hypoxia stimulate the secretion of this hormone [18].

Increased levels of NT-proBNP and their association with undesirable outcomes in patients with COVID-19 were reported in several studies. In the study designed by Gao et al. [3], higher levels of NT-proBNP in patients with COVID-19 were found to be related to a lower cumulative survival rate and its prognostic effect might be a specific index reflecting the overall state of SARS-CoV-2 infection. In the literature there are many studies demonstrating a high positive correlation between troponin and NT-proBNP levels in COVID-19 patients. In an analysis including 416 patients hospitalized with COVID-19, NT-proBNP levels were significantly higher among patients with myocardial injury than those without [19]. Wang et al. [6] argued that NT-proBNP has a critical role in estimating cardiac risk stratification and

the prognosis of patients with severe COVID-19. Jin et al. [20] compared the NT-proBNP levels in patients with COVID-19 who developed cardiac injury and those who did not, demonstrating that patients with cardiac injury were more likely to have elevation of NT-proBNP at a rate of 66.7% in comparison to 10% among those without cardiac injury. Our results also demonstrate a statistically significant increase in NT-proBNP levels in patients with COVID-19 compared to a healthy population.

Different types of markers were defined as predictors of inflammation and cardiovascular risk in several studies, such as proinflammatory cytokines, adhesion molecules, oxidized low-density lipoproteins, acute phase reactants, white blood cells, and erythrocyte sedimentation rate [21]. In addition to these markers, the Neut/Lym, Lym/Mono, and Plt/Lym ratios are novel biomarkers used as indicators of inflammation [5].

The Neut/Lym ratio is a fast, easy, and inexpensive method for the assessment of inflammatory status and has been recently introduced as a biomarker for the investigation of cardiovascular risk. This marker is obtained by calculating the ratio of absolute neutrophil count to absolute lymphocyte count [5]. The association between the Neut/Lym ratio and COVID-19 has been examined in the literature and a higher Neut/Lym ratio was found to be an independent risk factor for in-hospital mortality among COVID-19 patients. In a study of 125 patients with COVID-19, it was hypothesized that an elevated Neut/Lym ratio would be a prognostic indicator of mortality in the COVID-19 patient population [22]. In our study, Neut/Lym values were statistically significantly higher in patients with COVID-19 than in the control group.

The Lym/Mono ratio is another novel systemic inflammation marker that is reproducible and widely available in clinical practice. It is obtained by calculating the ratio of absolute lymphocyte count to absolute monocyte count [5]. In a study conducted by Lissoni et al. [23], 71% of patients with COVID-19 had lower Lym/Mono ratios when compared to control subjects, and the authors indicated that Lym/Mono is a simple and less expensive biomarker that can be used in the clinical evaluation of COVID-19 infection. Shivakumar et al. [24] compared Lym/Mono ratios between survivors and nonsurvivors among patients with COVID-19 and found that Lym/Mono was lower in the nonsurvivors. Our study revealed statistically significantly lower values of Lym/Mono ratios in patients with COVID-19 than the control group.

The Plt/Lym ratio is also a fast, broadly available, and cheap marker that can be used in the evaluation of inflammation and atherosclerosis. It is calculated as the ratio of absolute platelet count to absolute lymphocyte count [5]. Wang et al. [25] evaluated Plt/Lym ratios in a study of 131 patients and explored the association between higher Plt/Lym ratios and mortality in COVID-19 due to aggregation disorders occurring in vascular structures. The relationship between Plt/Lym ratio and the severity of COVID-19 was revealed in that meta-analysis, which included 998 patients. In our study, the Plt/Lym ratio was likewise higher in the group of patients with COVID-19 than the control group.

### Conclusion

Patients with COVID-19 are prone to developing cardiac

morbidities and mortality with different mechanisms. NT-proBNP and the Neu/Plt, Lym/Mono, and Plt/Lym ratios are important cardiovascular markers that can be used for close follow-up in hospitalized patients infected with SARS-CoV-2 and they may help clinicians adopt optimal treatment strategies in early stages to prevent probable cardiovascular events.

#### Acknowledgment

Abdullah Tuncay Demiryurek assessed the language of the article.

#### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

#### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

**Funding:** None

#### Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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#### How to cite this article:

Ozgur Altinbas, Ayse Ozlem Mete, Seniz Demiryurek, Erhan Hafiz, Ahmet Saracaloglu, Abdullah Tuncay Demiryurek. Relationships between NT-proBNP and novel biochemical parameters and increased cardiovascular risk in COVID-19. *Ann Clin Anal Med* 2021; 12(Suppl 4): S529-533